

Application Serial No.: 10/076,071
Amendment dated December 20, 2004
Reply to Office Action of September 24, 2004

Amendments to the Specification:

Replace the paragraph which begins at line 4 on page 1 and ends at line 10 on page 1 of the application with the following amended paragraph:

This application is a continuation-in-part of pending application 09/678,202, filed September 29, 2000. This application also claims benefit of provisional applications 60/283,507, filed April 11, 2001, 60/281,648, filed April 4, 2001, ~~60/_____~~, (originally given application number ~~09/816,679~~), 60/509,045, filed March 22, 2001, 60/157,404, filed October 1, 1999, 60/211,078, filed June 13, 2000, and 60/268,558, filed February 13, 2001. The entire disclosure of the aforementioned applications is considered to be part of the disclosure of this application and is hereby incorporated by reference.

Replace the paragraph which begins at line 3 on page 6 and ends at line 22 on page 6 of the application with the following amended paragraph:

The ATCUN motif has been found in other naturally-occurring proteins besides albumins, and non-naturally-occurring peptides and proteins comprising the ATCUN motif have been synthesized. See, e.g., Harford and Sarkar, *Acc. Chem. Res.*, **30**, 123-130 (1997); Bal et al., *Chem. Res. Toxicol.*, **10**, 906-914 (1997); Mlynarz, et al., *Speciation 98: Abstracts*, <http://www.jate.u-szeged.hu/~spec98/abstr/mlynarz.html>. Cu(II) and Ni(II) complexes of ATCUN-containing peptides and proteins have been reported to exhibit superoxide dismutase (SOD) activity. See Cotelle et al., *J. Inorg. Biochem.*, **46**, 7-15 (1992); Ueda et al., *J. Inorg. Biochem.*, **55**, 123-130 (1994). Despite their reported SOD activity, these complexes still produce free radicals which damage DNA, proteins and other biomolecules. See Harford and Sarkar, *Acc. Chem. Res.*, **30**, 123-130 (1997); Bal et al., *Chem. Res. Toxicol.*, **10**, 915-21 (1997); Ueda et al., *Free Radical Biol. Med.*, **18**, 929-933 (1995); Ueda et al., *J. Inorg. Biochem.*, **55**, 123-130 (1994); Cotelle et al., *J. Inorg. Biochem.*, **46**, 7-15 (1992). As a consequence, it has been hypothesized that at least some of the adverse effects of copper and nickel *in vivo* are attributable to the binding of Cu(II) and Ni(II) to ATCUN-containing proteins

which causes the production of damaging free radicals. See Harford and Sarkar, *Acc. Chem. Res.*, **30**, 123-130 (1997); Bal et al., *Chem. Res. Toxicol.*, **10**, 915-921 (1997); Cotellet et al., *J. Inorg. Biochem.*, **46**, 7-15 (1992). Cf. Koch et al., *Chem. & Biol.*, **4**, 549-60 (1997). The damaging effects produced by a Cu(II) complex of an ATCUN-containing peptide have been exploited to kill cancer cells *in vitro* and to produce anti-tumor effects *in vivo*. See Harford and Sarkar, *Acc. Chem. Res.*, **30**, 123-130 (1997).

Replace the paragraph which begins at line 6 on page 16 and ends at line 25 on page 16 of the application with the following amended paragraph:

The sequences of many peptides which comprise a binding site for transition metal ions are known. See, e.g., U.S. Patents Nos. 4,022,888, 4,461,724, 4,665,054, 4,760,051, 4,767,753, 4,810,693, 4,877,770, 5,023,237, 5,059,588, 5,102,990, 5,118,665, 5,120,831, 5,135,913, 5,145,838, 5,164,367, 5,591,711, 5,177,061, 5,214,032, 5,252,559, 5,348,943, 5,443,816, 5,538,945, 5,550,183, 5,591,711, 5,690,905, 5,759,515, 5,861,139, 5,891,418, 5,928,955, and 6,017,888, PCT applications WO 94/26295, WO 99/57262 and WO 99/67284, European Patent application 327263, Lappin et al., *Inorg. Chem.*, **17**, 1630-34 (1978), Bossu et al., *Inorg. Chem.*, **17**, 1634-40 (1978), Chakrabarti, *Protein Eng.*, **4**, 57-63 (1990), Adman, *Advances In Protein Chemistry*, **42**, 145-97 (1991), Cotellet et al., *J. Inorg. Biochem.*, **46**, 7-15 (1992), Canters et al., *FEBS*, **325**, 39-48 (1993), Regan, *Annu. Rev. Biophys. Biomol. Struct.*, **22**, 257-281 (1993), Ueda et al., *J. Inorg. Biochem.*, **55**, 123-30 (1994), Ueda et al., *Free Radical Biol. Med.*, **18**, 929-33 (1995), Regan, *TIBS*, **20**, 280-85 (1995), Ueda et al., *Chem. Pharm. Bull.*, **43**, 359-61 (1995), Bal et al., *Chem. Res. Toxicol.*, **10**, 906-914 (1997), Bal et al., *Chem. Res. Toxicol.*, **10**, 915-21 (1997), Koch et al., *Chem. Biol.*, **4**, 549-60 (1997), Kowalik-Jankowska et al., *J. Inorg. Biochem.*, **66**, 193-96 (1997), Harford and Sarkar, *Acc. Chem. Res.*, **30**, 123-130 (1997), Prince et al., *TIBS*, **23**, 197-98 (1998), Mlynarz, et al., *Speciation 98: Abstracts*, <http://www.jate.u-szeged.hu/~spec98/abstr/mlynar.html>, and Aitken, *Molec.*

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Biotechnol., **12**, 241-53 (1999), Whittal et al., *Protein Science*, **9**, 332-343 (2000). P₂ may comprise the sequence of one or more of the metal-binding sites of these peptides.

Replace the paragraph which begins at line 22 on page 39 and ends at line 3 on page 40 of the application with the following amended paragraph:

An angiogenic disease or condition is a disease or condition involving, caused by, exacerbated by, or dependent on angiogenesis. Angiogenesis is the process of new blood vessel formation in the body. Copper is required for angiogenesis. See PCT application WO 00/21941 and "The Role Of Copper In The Angiogenesis Process (http://www.cancerprotocol.com/role_of_copper.html, 1/28/02), and references cited in both of them. In particular, copper is involved in the activation of growth factors (such as the dimerization of b-FGF and serum Cu²⁺-GHK), activation of angiogenic factors (such as Cu²⁺-(K)GHK derived from SPARC), cross-linking of the transitional matrix (e.g., collagens VIII and I by Cu²⁺-dependent lysyl oxidase), and formation of basement membrane (e.g., collagens IV and elastin by Cu²⁺-dependent lysyl oxidase).